CHLOROTHIAZIDE IN HYPERTENSIVE AND NORMOTENSIVE PATIENTS

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Chlorothiazide was synthesized by Novello and Sprague[1] and found to be a potent, orally effective diuretic and saluretic agent by Beyer, Baer, Russo, and Haimbach.[2] Ford, Moyer, and Spurr[3] have reported on its diuretic and saluretic properties in patients with edema. Because of its pronounced saluretic action a clinical trial of this agent was undertaken in hypertensive patients.

The present report covers our experience to date in 105 patients, 90 of whom were hypertensive. In the beginning our major interest was in the attempt to potentiate the action of other antihypertensive drugs. A summary of early results was submitted as an abstract to the American Heart Association, Inc., New York, N.Y.,[4] in June 1957, and a preliminary note was published in the Medical Annals of the District of Columbia in September 1957.[5]

Thus far, a total of 73 patients under prior treatment with various antihypertensive agents have had chlorothiazide added to their regimens. The period of observation prior to the administration of chlorothiazide averaged two years, and the period of chlorothiazide therapy has averaged 3.5 months, with a range of 1 to 8 months. For the most part these patients represented moderately severe to severe phases of the disease, although the range varied from very mild to the malignant phase.

Thirty-three patients had been on a regimen including the ganglionic blocking agents pentolinium (Ansolysen), mecamylamine (Inversine), and chlorisondamine (Ecolid), both alone and in various combinations with reserpine and hydralazine (Apresoline). There also was a group of 19 patients under treatment with the *Veratrum* alkaloids, either alone or in combination with other drugs, and 21 patients treated with reserpine or with reserpine and hydralazine (TABLE 1).

The reduction in blood pressure after these various treatment regimens varied from good to poor in individual cases and, for the group as a whole, averaged 11 per cent below the control level. After the addition of chlorothiazide there was a prompt further reduction in blood pressure in 68 patients, with an average reduction of 27 per cent from control or pretreatment levels. Thus, the additional percentage of reduction observed after exhibition of chlorothiazide averaged 16 per cent.

The average control blood pressure for the entire group before any therapy was 211 systolic and 126 diastolic; after chlorothiazide plus other antihypertensive regimens, it was 153 systolic and 98 diastolic.

The dosages of ganglionic blocking agents had been reduced in 13 of these cases and omitted entirely in 19 others, but with continued administration of reserpine and/or hydralazine. Indeed, it was essential to reduce the dosage of the ganglionic blocking agents in order to avoid marked postural hypotension.

TABLE 1

ADDITION OF CHLOROTHIAZIDE TO OTHER ANTIHYPERTENSIVE REGIMENS

Antihypertensive regimen	No. pts.	Average blood pressure before drug		Per cent change in blood pressure		
		Syst.	Dias.	Before chloro-thiazide	After chloro-thiazide	Difference
Ganglionic blocking agent	10	225	135	−12.5	−28.7	−16.2
Ganglionic blocking agent and reserpine	12	214	130	−9.6	−25.7	−16.1
Ganglionic blocking agent, reserpine, and hydralazine	8	236	134	−20.9	−34.8	−13.9
Ganglionic blocking agent and hydralazine	3	203	115	−7.5	−18.3	−10.8
Veratrum	5	210	120	−9.7	−25.4	−15.7
Veratrum and reserpine	12	208	122	−6.8	−22.6	−15.8
Veratrum, reserpine, and hydralazine	2	240	152	−15.6	−32.9	−17.3
Reserpine	7	175	120	−12.3	−26.2	−13.9
Reserpine and hydralazine	14	198	118	−8.9	−28.3	−19.4
Total	73					
Mean		211	126	−11.0	−27.0	−16.0

Five additional patients who had been subjected to lumbodorsal sympathectomy in the past were given chlorothiazide alone. Following the drug there was a reduction of blood pressure averaging 21 per cent.

Chlorothiazide also has been given in combination with parenteral reserpine and hydralazine to two patients with far-advanced malignant hypertension and uremia. Rapid progression of the renal failure and death were not prevented in either case.

An attempt was made to withdraw all other medication except chlorothiazide in 32 patients (TABLE 2). The blood pressure remained essentially unchanged in 10 of these cases. In 22 patients there was a rise of 10 per cent or more in the diastolic and, in 6 of these, the elevation has proceeded to the control or pretreatment level. The elevation of blood pressure began in 1 to 8 days after discontinuation of the other antihypertensive agents. Thus, in approximately one third of the patients the antihypertensive effect was as marked on chlorothiazide alone as it was on combined therapy.

It was now apparent that, in addition to its potentiating action, chlorothiazide is a hypotensive agent in its own right. Decreases in blood pressure also were seen in hypertensive patients who were being given chlorothiazide alone for various experimental procedures.

An experiment was set up, therefore, to determine the extent of its antihypertensive effect under carefully controlled conditions. Accordingly, 10 previously untreated, hospitalized, nonedematous hypertensive patients were placed on a diet containing 1.25 gm. of salt per day and, in addition, were given a supplement of 3 gm. of salt daily in tablet form (TABLE 3). This provided a relatively stable salt intake of approximately 4 gm. daily regardless of any possible change in the patient's appetite.

After the diet had been established for several days, the blood pressure was

TABLE 2

EFFECTS ON BLOOD PRESSURE OF DISCONTINUING ALL MEDICATIONS EXCEPT CHLOROTHIAZIDE

Number of patients with other agents discontinued	32
Blood pressure unchanged	10
Some elevation (>10% diastolic)	22
Elevation to predrug level	6

Elevation began 1 to 8 days after discontinuation.

TABLE 3

EFFECTS ON BLOOD PRESSURE AFTER EXHIBITION OF CHLOROTHIAZIDE ALONE IN 10 PREVIOUSLY UNTREATED HOSPITALIZED PATIENTS UNDER CONSTANT CONDITIONS OF SALT INTAKE

10 Hospitalized hypertensive patients
Diet, 500 mg. sodium (1.25 gm. as NaCl)
Supplement: 3 gm. NaCl daily in tablets
6 Days control, then 6 days chlorothiazide (1.5 gm. daily)
Change in systolic blood pressure: mean = 18% (range 10 to 37%) fall
Change in diastolic blood pressure: mean = 9.5% (range 5 to 20%) fall
Average fall "mean" blood pressure: 16% (range 9 to 25%)
Time required for blood pressure to fall to new level: 1 to 3 days

recorded by one of us twice daily for a 6-day period and, if it was stable, the patient was then given chlorothiazide (1.5 gm. daily) in 3 divided doses with continued measurement of blood pressure for an additional 6 days. The blood pressures recorded during the last 3 days of the control period and the last 3 days of the treatment period were averaged separately and compared.

The results showed some decline in blood pressure in every case. The systolic fall averaged 19 per cent with a range of 10 to 37 per cent. The diastolic reduction averaged 14 per cent with a range of 5 to 20 per cent. The fall in mean blood pressure (that is, systolic plus diastolic divided by 2) ranged between 9 and 25 per cent with a mean of 17 per cent.

The time required for the blood pressure to fall to the new level was only 1 to 3 days. In 5 of these patients chlorothiazide was withdrawn after the sixth day, and the blood pressures returned to control levels in 1 to 4 days. Chlorothiazide was continued in 3 other patients whose blood pressure had fallen, but the salt intake was raised from 4 to 11 gm. daily by increasing the dosages of the salt tablets. Arterial pressure rose significantly after the increased salt intake in all 3 instances (FIGURE 1). In 2 additional patients it was necessary to elevate the salt intake to 20 gm. before a significant rise in blood pressure occurred.

Of great interest also has been the observation that, in 15 nonedematous *normo*tensive patients followed under exactly similar dietary and hospital control conditions, no reduction of arterial pressure occurred following chlorothiazide. Thus, in the dosages used the antihypertensive effects of chlorothiazide seems to be limited to the hypertensive state.

The urinary excretions of chloride, sodium, and potassium were measured under balance conditions in 4 nonedematous hypertensive patients. The daily intake of sodium and chloride was 75 mEq. FIGURE 2 demonstrates a marked chloruresis and natriuresis, with a lesser potassium excretion tapering off toward

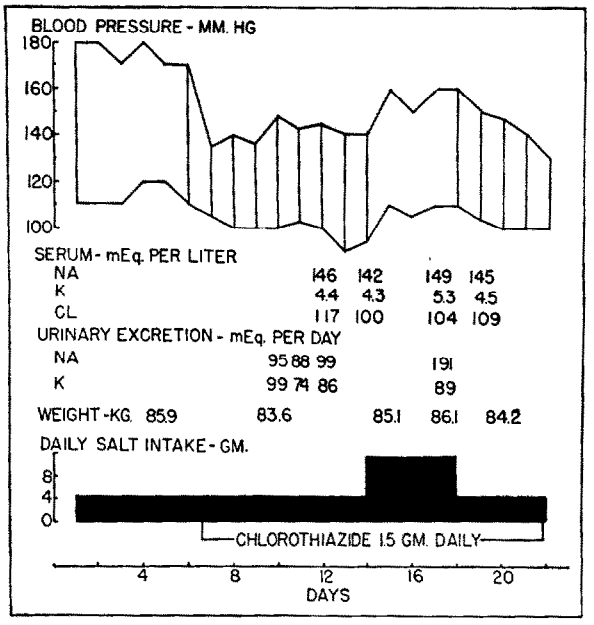

FIGURE 1. Effects on blood pressure, serum concentrations of sodium, potassium, and chloride, body weight, and the urinary excretion of sodium and potassium in a chlorothiazide-treated hypertensive patient in whom the salt intake was raised from 4.25 to 11.25 gm. daily.

the base line after several days. There was no significant change in the serum electrolytes.

It is also of interest to review briefly some other observations. Weight loss usually was not marked, and often was transient. The electrocardiogram showed no significant changes other than the decrease in LVH pattern frequently seen with other antihypertensive drugs. Except for a slight downward trend for sodium, the serum concentrations of sodium and chloride have shown no marked change after months of treatment. Serum potassium concentrations often decrease, but not to levels below 3 mEq. per liter. A decrease in plasma volume of 5 to 30 per cent and a compensatory rise in hematocrit occur, as has been noted also by H. P. Dustan and her co-workers (personal communication). This appears to be a reflection of a decrease in total extracellular fluid space, since the radiosodium space also decreases. The latter observations will be reported in detail elsewhere.[6]

The side effects were few and mild in nature. Six patients complained of nausea and 3 of weakness during the first month of treatment; discontinuation of the drug for 1 day promptly cleared these symptoms. Chlorothiazide will exaggerate postural hypotension if already present, but will not produce it *de novo*. In general the patients looked and felt exceedingly well while taking the drug. Improvement in physical and mental vigor was especially marked in the group in whom ganglionic blocking agents could be discontinued and in patients with latent or overt congestive failure.

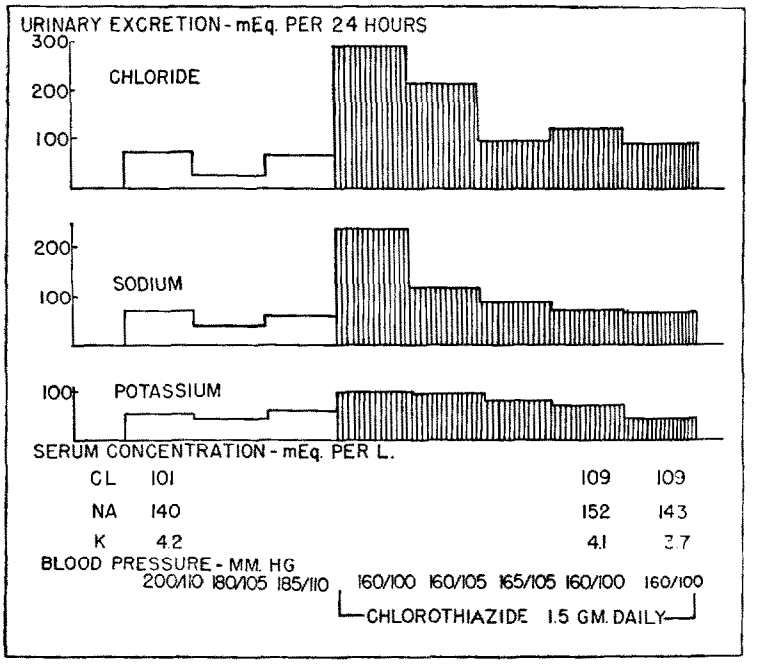

FIGURE 2. Changes in urinary excretion and serum concentrations of chloride, sodium, and potassium, and in blood pressure after 1.5 gm. of chlorothiazide daily. Salt intake was maintained at 4.25 gm. daily throughout this period.

At this stage it is premature to do more than speculate on the mode of action of chlorothiazide. However, two observations seem worthy of special comment. One is that chlorothiazide did not reduce blood pressure in normotensive individuals; the other is the preliminary observation that an excess of salt may combat the antihypertensive effect of chlorothiazide in hypertensive patients. These observations again focus attention on the relationship between salt balance and hypertension. Through its potent saluretic effect chlorothiazide may become a valuable tool in exploring that relationship.

Until more experience is gained with chlorothiazide the possibility of precipitating serious electrolyte imbalance must be kept in mind as an ever-present danger. Electrolyte disturbances have been reported in nonhypertensive patients maintained on higher dosages; that is, 2 to 3 gm. per day (J. R. Beem, personal communication). Protracted vomiting or diarrhea conceivably could easily precipitate electrolyte imbalance in patients taking chlorothiazide, and the same dangers would apply in patients with renal failure. As with other effective agents, the potentialities of this potent drug must be treated with respect.

In conclusion, the experience to date in 88 hypertensive and 15 normotensive patients indicates that chlorothiazide is an effective and well-tolerated antihypertensive agent that appears to be specific for the hypertensive state.

Its mode of action appears to differ from those available heretofore. It produces significant reduction of blood pressure when used alone and additional reduction when combined with other antihypertensive agents or when given to sympathectomized patients. Finally, we should like to stress that eight months is too short a period within which to judge the effects of any therapeutic regimen in hypertension or to be certain that the drug may not have long-term toxic effects that we do not yet suspect.

References

1. NOVELLO, F. C. & J. M. SPRAGUE. 1957. Benzothiadiazine dioxides as novel diuretics. J. Am. Chem. Soc. **79:** 2028.
2. BEYER, K. H., J. E. BAER, H. F. RUSSO & A. HAIMBACH. 1957. Chlorothiazide (6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide): the enhancement of sodium chloride excretion. Federation Proc. **16:** 282.
3. FORD, R. V., J. H. MOYER & C. L. SPURR. 1957. Clinical and laboratory observations on chlorothiazide, an orally effective nonmercurial diuretic agent. A.M.A. Arch. Internal Med. **100:** 582–596.
4. FREIS, E. D., I. M. WILSON & A. E. PARRISH. 1958. Enhancement of antihypertensive activity with chlorothiazide. Circulation. In press.
5. FREIS, E. D. & I. M. WILSON. 1957. Potentiating effect of chlorothiazide (Diuril) in combination with antihypertensive agents. Preliminary Report. Med. Ann. Dist. Columbia. **26:** 468.
6. FREIS, E. D., I. M. WILSON, H. W. SCHNAPER & A. WANKO. In preparation.